Itch, sneeze and wheeze: the genetics of atopic allergy

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J R Soc Med 2002;**95**:14–17

In many developed countries over one-fifth of the population are affected by one or more atopic allergic disorders. Several time-trend studies indicate that the prevalence and severity of eczema, rhinitis, and asthma is rapidly increasing[1–3]; and this observation, coupled with the widespread geographical variations in disease prevalence noted by the International Studies of Asthma and Allergies in Childhood, points to the strong contribution of environment to the aetiology[4]. However, the tendency of atopic allergic conditions to cluster both within individuals and within families suggests that genetic factors are also important.

Asthma is a condition characterized by reversible airflow obstruction and lower airway hyper-responsiveness, which results in episodic cough, wheeze and shortness of breath[5]. Inflammation of the nasal passages, manifesting as sneezing, nasal blockage and itchy rhinorrhoea, is the symptom complex known as rhinitis[6]. Eczema is the commonest cause of dermatitis in developed countries and affects approximately 20% of the general population[7]. The distribution of eczematous lesions varies with age, the face and trunk being most affected in infants whereas the flexor aspects of the limbs are typically affected in older children and adults. Advances in our understanding of the immunobiology of these disorders have shown them to have a common pathophysiological basis—an exaggerated and inappropriate IgE-mediated inflammation in response to allergen exposure—referred to as atopy[8]. The absence of objective and reliable criteria for defining either atopy or the atopic allergic conditions (eczema, rhinitis and asthma) has been and continues to be a major obstacle to establishing the genetic basis of atopic disorders.

This review is based in the main on articles retrieved by searching Medline, EMBASE and OMIM (Online Mendelian Inheritance in Man) electronic databases. Key websites of possible relevance were also searched[9], including those of the British Society for Human Genetics[10], the European Society for Human Genetics[11], and the Human Mutation Database[12]. Allergy and genetic texts were consulted, and the analysis was helped by personal contacts with several experts on human genetics.

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FAMILIAL STUDIES

Evidence for familial clustering

Anecdotal evidence for familial clustering of atopic disorders dates back to the early twentieth century[13]. More rigorous evidence emerged in the latter half of the century, when many studies showed that relatives of atopic patients had a higher prevalence of atopic allergic disorders than did relatives of matched non-atopic patients[14]. Research subsequently revealed that atopic individuals and couples were substantially more likely than non-atopics to give birth to children with one or more atopic disorders[15]. Although these findings provided strong and consistent evidence for the importance of shared familial characteristics, they were in themselves insufficient to prove genetic causation.

Studies in twins are a good way to disentangle genetic and environmental factors in families, and early work in small numbers showed that concordance rates for atopic disorders were higher for monozygotic (MZ) than for dizygotic (DZ) twins[14]. These findings were replicated in several larger studies conducted in various population groups. The most notable was Edfors-Lubs's study of 7000 Swedish twin pairs, in which the MZ *versus* DZ concordance rates were: asthma 19.0% *vs* 4.8%; rhinitis 21.4% *vs* 13.6%; eczema 15.4% *vs* 4.5%[16]. Work by Hanson and colleagues, comparing serum IgE levels in MZ and DZ twins reared together and apart, was another landmark in familial studies: MZ twins had consistently stronger correlation coefficients for serum total IgE than did DZ twins[17]. In addition, MZ twins showed over 70% concordance for specific IgE response to one or more common aeroallergens; however, the finding that almost one-third of MZ twins were discordant indicated that sensitization through environmental exposure was also aetiologically important.

Segregation analysis

Segregation analysis, or the study of trait distributions in families, has often been a key step in elucidating the genetic basis for disease, allowing testing to see whether the pattern of phenotype distribution within families is consistent with a known genetic model[18]. But in common multifactorial and

heterogeneous disorders this can be a hazardous undertaking. Results to date from such studies have been inconsistent and confusing. Using complex segregation analysis techniques for studying IgE concentrations in 173 families, Gerard and colleagues concluded that the regulatory locus for IgE occupied two alleles, with the dominant allele suppressing persistently high levels of IgE[19]. The observation that 90% of atopic asthmatics in 239 members of forty nuclear families had an atopic parent led Cookson and Hopkin to suggest a dominant model of inheritance for propensity to produce an exaggerated IgE response[20]. Other Mendelian models proposed have included autosomal recessive inheritance, autosomal dominant inheritance with incomplete penetrance, co-dominance, and dominant inheritance through the maternal line[21]. Opinion has lately converged on the view that several genes interact to determine liability to disease (polygenic inheritance). Empirical support for this suggestion comes from the findings of Xu and colleagues, who, studying serum total IgE data in 92 Dutch families, found that two-locus segregation analysis gave a better fit than did a one-locus model[22].

An additional layer of complexity comes from the increasing evidence that inheritance of atopic disorders is end-organ specific—i.e. for the skin (eczema), nose (rhinitis) and airways (asthma)[23]. The possibility is thus raised that, although inheritance of an exaggerated IgE response may underlie all these conditions, separate genes predispose to specific clinical manifestations of the allergic phenotype.

GENE MAPPING STUDIES

Genes responsible for causing disease may be identified by determining loci of interest through positional cloning analysis or by the examination of candidate genes. The former involves demonstration of co-inheritance of possible disease genes with known chromosomal markers, whereas the latter involves determination of the role of genes for specific proteins known to be important in pathogenesis.

Positional cloning analysis

The first evidence for linkage of atopy to a specific chromosomal region was made in 1989 when Cookson and colleagues detected linkage disequilibrium with the D11S97 marker implicating chromosome 11q13[24]. Seven families were studied in total and a maximum LOD score of 5.6 was obtained (LOD score is the logarithm of the odds ratio of the probability of observing such a family if the genes are linked compared with the probability of observing such a family if the genes are not linked; a score of >3 is generally considered to provide evidence of linkage). In this dataset, a large part of the score came from a single family, and attempts at replication have yielded inconsistent results. Positive linkages have been noted in studies conducted in the Netherlands, Germany, Japan, and Australia, for example[25]; but a large British study, in which atopy was characterized as a continuous variable, produced no evidence of linkage at this site[26].

Another region of intense interest is chromosome 5q, which contains several candidate genes for atopy including those that encode for cytokines known to be important in pathogenesis (IL-3, IL-4, IL-5, IL-9, IL-12, IL-13) as well as those that encode for the β_2-adrenergic receptor, the corticosteroid receptor and the granulocyte-macrophage colony-stimulating factor. Marsh and colleagues reported linkage of 5q markers with atopy in a US Amish population[27] and Meyers *et al.*[28] have replicated their findings in a group of Dutch families; but not all groups have been as successful[25]. Linkages have been found with several other loci including chromosomes 13q, 12q and 6p, although replication has again proved problematic. So far, four genome-wide screening studies for atopic disorders have been reported, and together they implicate a total of thirteen chromosomes (1, 4, 5, 6, 7, 11, 12, 13, 14, 16, 17, 19 and 21); however, replication has been possible only with respect to chromosomes 4, 7, 11 and 16[25].

Why has replication proved so troublesome? Clearly there are inherent difficulties in studying complex genetic disorders in which environmental factors are also important[29]. Biases in the selection of subjects and a failure to correct for multiple testing will increase the possibility of type 1 errors; and type 2 errors will be fostered by disagreement amongst research teams on definitions of atopy and atopic allergic conditions, and by the small sample sizes frequently used. Another important factor, yet to be resolved, is the question of a significant LOD[29]. Conventional cut-off values of >3 for detecting significance at the 5% level are likely to generate many false-positive linkages when complex genetic disorders are studied. For example, Daniels *et al.*, in their genome screen of eighty nuclear families with 300 markers spaced at approximately 10% recombination, opted for a significance level of 0.1%; nonetheless, Monte Carlo simulations indicated that 1.6 false-positive linkages were to be expected from the data[30]. The American Collaborative Study on the Genetics of Asthma used a significance level of 1%, and this almost certainly explains the unexpectedly large number of linkages detected[31].

Candidate genes

Characterization of many of the inflammatory mediators crucial to pathogenesis, and the sequencing and cloning of several of the responsible genes, has made possible the testing of candidate genes for atopy. The principal difficulty

herein is that the list of candidate genes is very long. Barnes and Page, for example, estimate that over a hundred inflammatory mediators may be involved in the pathogenesis of asthma alone, implicating a similar number of candidate genes[32].

A comprehensive review of the candidate genes thus far considered empirically is beyond the scope of this paper. Suffice it to say that associations have been detected with several genes of interest including most notably the cytokines encoded for on chromosome 5q (see above) and the FceR1B gene on chromosome 11q13 that codes for the beta-chain of the high-affinity IgE receptor gene[33]. Mutations of the latter could conceivably lead to increased signal transduction after allergen binds to IgE. One such mutation, Leu-181, has been shown to be associated with atopy and asthma in some populations but not others. Another substitution in this gene results in an aminoacid substitution (Glu237Gly) in the region encoding for the cytoplasmic tail of the protein, and this too is associated with positive skin tests and childhood asthma in some population groups[25].

CONCLUSIONS

Family studies suggest that atopic disorders result from a complex interplay between genetic and environmental factors; a fuller appreciation of the precise nature of these interactions will prove crucial to the development of primary prevention strategies for eczema, rhinitis and asthma. Identification of the responsible genes is difficult because of the conceptual and methodological obstacles to study of complex genetic disorders. Progress will be crucially dependent on agreement between clinicians and researchers on phenotypic characteristics for disease that have biological plausibility; one possible strategy that has yet to be adequately considered is the use of quantitative phenotype scores for atopy and atopic allergic conditions—an approach that would avoid the somewhat arbitrary dichotomization of data. There is still no consensus on the LOD score values that should be regarded as significant for non-Mendelian conditions, but wider appreciation of the risk of detecting false-positive linkages with conventional cut-off values should lead to greater caution in interpretation of data. Statistical advances also raise the possibility of pooling data from several linkage studies—a strategy that would reduce greatly the risk of type 2 errors. Despite these reservations, it is clear that there are now several loci that represent sites of great interest to those investigating the aetiology of atopy; these include 5q (IL4/IL5 cytokine cluster), 6p (HLA and TNF), 11q (FceR1B), and 13q and 14q (TCR-alpha). If the genetic risk can be narrowed to a reasonable number of loci, exciting prospects will be opened for diagnosis, therapeutics and, above all, prevention.

Acknowledgments I thank the Genetic Epidemiology Unit at the London School of Hygiene and Tropical Medicine for many critical discussions and Professor Stephen Durham for constructive comments. I am supported by a NHS R&D National Primary Care Award.

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